

UCSF

UC San Francisco Previously Published Works

Title

Clinical Utility of Echocardiography in Former Preterm Infants with Bronchopulmonary Dysplasia.

Permalink

<https://escholarship.org/uc/item/01x970t1>

Journal

Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography, 33(3)

ISSN

0894-7317

Authors

Nawaytou, Hythem
Steurer, Martina A
Zhao, Yili
[et al.](#)

Publication Date

2020-03-01

DOI

10.1016/j.echo.2019.10.012

Peer reviewed

Clinical Utility of echocardiography in former preterm infants with bronchopulmonary dysplasia

Nawaytou: Echo-Cath agreement in BPD

Hythem Nawaytou¹, Martina A. Steurer^{a,b}, Yili Zhao^a, Elyssa Guslits^a, David Teitel^a, Jeffrey R. Fineman^a, Roberta L. Keller^a

Affiliations: ^a Department of Pediatrics, *University of California, San Francisco*, ^b Department of Epidemiology and Biostatistics, *University of California, San Francisco, CA*

Authors' emails: hythem.nawaytou@ucsf.edu, Martina.Steurer@ucsf.edu, Yili.Zhao@ucsf.edu, Elyssa.Guslits@ucsf.edu, David.Teitel@ucsf.edu, Jeffery.Fineman@ucsf.edu, Robert.Keller@ucsf.edu

Address of Correspondence:

Hythem Nawaytou, MBBCH, MSc
550 16th St
Box 0544
San Francisco, Ca 94158

Abstract

BACKGROUND: The clinical utility of echocardiography for the diagnosis of pulmonary vascular disease (PVD) in former preterm infants with bronchopulmonary dysplasia (BPD) is not established. Elevated pulmonary vascular resistance (PVR) rather than pulmonary artery pressure (PAP) is the hallmark of PVD. We evaluated the utility of echocardiography in infants with BPD in diagnosing pulmonary hypertension and PVD (PVR >3 woods units \times m^2) assessed by cardiac catheterization.

METHODS: A retrospective single center study of 29 infants born ≤ 29 weeks gestational age with BPD who underwent cardiac catheterization and echocardiography was performed. PVD was considered present by echocardiography if the tricuspid valve regurgitation jet peak velocity was >2.9 m/sec, post-tricuspid valve shunt systolic flow velocity estimated a right ventricular systolic pressure >35 mmHg or systolic septal flattening was present. The utility (accuracy, sensitivity and specificity) of echocardiography in the diagnosis of PVD was tested. Subgroup analysis in patients without post tricuspid valve shunts was performed. Echocardiographic estimations of right ventricular pressure, dimensions, function and pulmonary flow measurements were evaluated for correlation with PVR.

RESULTS: The duration between echocardiography and cardiac catheterization was a median of 1 day (interquartile range: 1 - 4 days).

Accuracy, sensitivity and specificity of echocardiography in diagnosing PVD were 72%, 90.5% and 25%, respectively. Accuracy, sensitivity and specificity increased to 93%, 91.7% and 100% when infants with post tricuspid valve shunts were excluded. Echocardiography had poor accuracy in estimating the degree of PAP elevation by cardiac catheterization. In infants without post tricuspid valve shunts, there was moderate-to-good correlation between indexed PVR and right ventricular myocardial performance index (ρ : 0.89, $p=0.005$), systolic to diastolic time index (0.84, $p<0.001$), right to left ventricular diameter ratio at end systole (0.66, $p=0.003$) and pulmonary artery acceleration time (0.48, $p=0.05$).

CONCLUSIONS: Echocardiography performs well in screening for PVD in infants with BPD and may be diagnostic in the absence of a post tricuspid valve shunt. However, cardiac catheterization is needed to assess the degree of pulmonary artery pressure elevation and PVR. The diagnostic utility of echocardiographic measurements that correlate with PVR should be evaluated prospectively in this patient population.

KEYWORDS: bronchopulmonary dysplasia, echocardiography, prematurity, pulmonary hypertension, pulmonary vascular disease

Abbreviations

ASD: atrial septal defect
BPD: bronchopulmonary dysplasia
CO: cardiac output
FAC: fractional area change
IQR: interquartile range
LV: left ventricle
MPI: myocardial performance index
PA: pulmonary artery
PAAT: pulmonary artery acceleration time
PAP: pulmonary artery pressure
PDA: patent ductus arteriosus
PVD: pulmonary vascular disease
PVR: pulmonary vascular resistance
PVRi: pulmonary vascular resistance indexed to body surface area
 Q_p : pulmonary blood flow
 $Q_p:Q_s$: ratio of pulmonary blood flow to systemic blood flow
RA: right atrium
RV: right ventricle
RVET: right ventricular ejection time
SDI: systolic to diastolic time index
SPAP/SBP: ratio of systolic pulmonary artery pressure to systemic systolic blood pressure
TAPSE: tricuspid annular plane excursion
TDI: tissue Doppler imaging
TR: tricuspid valve regurgitation
VSD: ventricular septal defect
WHO: world health organization

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosures: None

Introduction

The gold standard for diagnosis of pulmonary arterial hypertension due to pulmonary vascular disease (PVD) is the cardiac catheterization derived calculation of pulmonary vascular resistance (PVR).¹ In former preterm infants diagnosed with bronchopulmonary dysplasia (BPD), elevated pulmonary artery pressure (PAP) diagnosed by echocardiography is associated with substantial risk of mortality.² Because cardiac catheterization is an invasive procedure, the American Heart Association¹ and the Pediatric Pulmonary Hypertension Network (PPHNet)³ have recommended performing echocardiograms as a less invasive tool to screen for the presence of PVD (indicated by elevated PAP) in patients with moderate or severe BPD. However, echocardiography does not measure PVR directly but rather uses blood flow velocities to estimate pulmonary artery pressure.⁴⁻⁷ PAP and PVR are related to each other through the equation: $\text{Pressure} = \text{Flow} \times \text{Resistance}$; thus elevated PVR is inferred by an elevated estimated PAP as long as pulmonary blood flow is not considered to be substantially elevated.

Prior studies have assessed the agreement and accuracy of estimated PAP by echocardiographic measurement of blood flow velocities and simultaneously measured PAP during cardiac catheterization in older children and young adults. This agreement has been found to be variable, with greater discrepancies at higher measured PAP.^{4,6,7} In younger children, Mourani and colleagues showed poor correlation between the PAP estimated by echocardiography from tricuspid regurgitant (TR) jet velocity to that

measured during cardiac catheterization in infants with chronic lung disease of various etiologies, although multiple echocardiographic abnormalities in combination with TR jet performed well with respect to prediction of pulmonary hypertension determined at cardiac catheterization.⁸ Due to the limitations described with estimating PAP by echocardiography, more recent investigations have evaluated pulmonary artery acceleration time (PAAT) for its accuracy in estimating PAP as well as PVR, as assessed by catheterization.⁹ PAAT was found to have strong agreement and accuracy for the diagnosis of pulmonary hypertension, although again, greater discrepancies occurred in actual measures of PAP and PVR when these values were more elevated.⁹

In this study, our goal is to measure the agreement between the echocardiographic assessment of right heart pressure and the pulmonary vascular bed, and the presence of elevated PVR on cardiac catheterization in former preterm infants with BPD, based on multiple quantitative and qualitative echocardiographic criteria that are known to reflect either PAP or PVR.

Methods

Subject Enrollment

At UCSF Benioff Children's Hospital, San Francisco, our practice is to screen premature infants with BPD for evidence of pulmonary hypertension by serial echocardiograms. If an echocardiogram shows evidence of

pulmonary hypertension despite optimization of the patient's respiratory support, the patient undergoes cardiac catheterization prior to starting pulmonary vasodilator medications. Pulmonary vasodilator therapy is started prior to cardiac catheterization only in cases where it is deemed life-saving or in patients that are referred from outside institutions already on pulmonary vasodilator therapy. Therefore, the population of patients undergoing cardiac catheterization would encompass patients with the spectrum of mild to severe pulmonary vascular disease. This is a single-center, retrospective cohort study. The cardiac catheterization lab database was reviewed for preterm infants born < 32wks gestational age who had undergone cardiac catheterization between July 2014 and December 2017. Patients with congenital heart disease other than atrial septal defect (ASD), ventricular septal defect (VSD) and persistent ductus arteriosus (PDA) were excluded. Each patient's electronic medical record was reviewed to identify those who have BPD, defined as an oxygen requirement at 36 weeks postmenstrual age ¹⁰ with an available echocardiogram proximate to the cardiac catheterization. Thirty former preterm infants with BPD had undergone cardiac catheterization during the study period. One infant was excluded because of an inadequate echocardiogram. The cohort consisted of twenty-nine infants born at a gestational age ≤ 29 weeks. We collected baseline demographics, pulmonary vasodilator therapy and the degree of respiratory support at the time of cardiac catheterization by review of the medical records. This study was approved by the University of California San

Francisco Institutional Review Board.

Echocardiograms

We analyzed the echocardiograms performed closest in time to the cardiac catheterizations. In patients who had an intervention (e.g. closure of an atrial septal defect (ASD) or a PDA), the echocardiogram performed prior to the intervention was analyzed. One investigator (Y.Z.), blinded to the results of the cardiac catheterizations, performed all of the echocardiographic measurements from stored examinations (*online supplement: Table 1*). All measurements were performed according to the American Society of Echocardiography guidelines on quantitative assessment in children.¹¹ To include a measurement of the peak velocity of the TR jet, two observers (Y.Z. and H.N.) had to agree that the Doppler envelope was at least 75% complete with a clear peak and start of deceleration. Pulmonary artery acceleration time and right ventricular ejection time were measured from a spectral pulse wave Doppler of the right ventricular outflow tract with clear valve spikes. In addition to measuring the right ventricular dimensions, we also collected qualitative assessments of the right ventricular size and hypertrophy from clinical reports.

In cases with cardiac shunts, we measured the size of the communication, the direction of blood flow and, for VSD or PDA, the systolic velocity of blood flow across the shunts. Peak VSD blood flow velocity was measured only when the flow occurred during the full duration of systole. An

ASD was defined as an inter-atrial communication larger than 3mm. The direction of flow in a shunt was determined using a combination of color Doppler and spectral Doppler assessments. For patients with a VSD or PDA, the systolic PAP was estimated by subtracting or adding ($4 \times$ systolic flow velocity²) from the systemic blood pressure if the systolic flow direction was left to right or right to left, respectively.^{4,12}

Estimation of the peak systolic PAP to systemic blood pressure (SBP) ratio (SPAP/SBP) was performed largely by using the RV systolic pressure estimate as a proxy for systolic PAP (as there was no RV outflow tract obstruction). We used multiple criteria including the peak TR jet velocity, the VSD or PDA systolic flow direction and peak velocity and the septal motion. The septal motion was graded as no systolic septal flattening (SPAP/SBP < 0.5), progressive systolic septal flattening (SPAP/SBP 0.5-0.80) and flattened septum throughout systole or bulging of the septum into the LV (SPAP/SBP >0.8)¹³ (Fig. 1) When criteria for assessment of PAP were discrepant, the criteria with the highest PAP estimation was used. An echocardiogram was considered positive for PVD if:

- TR jet velocity >2.9m/sec¹⁴, or
- VSD or PDA systolic flow velocity estimating peak systolic PAP > 35mmHg, or
- Systolic septal flattening was present

Pulmonary hypertension was graded on echocardiograms as no/mild (SPAP/SBP < 0.5), moderate (SPAP/SBP = 0.5-0.8) or severe (SPAP/SBP >

0.8) to allow grading of all patients including those with septal position as their only sign of pulmonary hypertension. We further analyzed measures of right ventricular dimensions, right ventricular systolic function and pulmonary flow dynamics to evaluate if additional echocardiographic features that correlate with pulmonary vascular resistance increase the diagnostic utility of the echocardiographic assessment.

Cardiac catheterizations:

Data collected at the time of cardiac catheterization included infant weight and age, indication for catheterization, level of respiratory support, type of anesthesia, and detailed hemodynamic data. Measurements of pressures were performed using fluid-filled catheters. The average of mean pulmonary artery pressure measurements in the right and left pulmonary arteries was used for calculations when available. Oxygen saturations and partial pressures were measured using blood samples from the different cardiac chambers. The dissolved oxygen content of blood was accounted for when the partial pressure of oxygen was greater than 100mmHg. Pulmonary and systemic blood flows were estimated by the Fick equation, using assumed oxygen consumption.¹⁶ The transpulmonary gradient was calculated by subtracting the left atrial pressure from the mean pulmonary artery pressure. The left atrial pressure was substituted by the pulmonary artery wedge pressure in two patients without an inter-atrial communication. PVR was calculated as the transpulmonary vascular pressure gradient divided by

the pulmonary blood flow and was indexed to body surface area (PVRi). We used two different sets of criteria to define the presence of PVD on cardiac catheterization. The first criterion was $PVRi \geq 3WU$ only, and the second was the updated WHO definition of pulmonary arterial hypertension (developed at the 6th World Symposium on Pulmonary Hypertension, Nice 2018), requiring $PVRi \geq 3WU$, mean PAP ≤ 20 mmHg and pulmonary artery wedge pressure ≤ 15 mmHg.¹⁵ We also repeated the analysis using the older WHO definition of pulmonary arterial hypertension ($PVRi > 3WU$, mean PAP ≥ 25 mmHg and pulmonary artery wedge pressure ≤ 15 mmHg)¹⁶ as this was the standard definition used at the time of these evaluations, to show the effect of the updated criterion on the accuracy of echocardiography. To grade the degree of PAP elevation during cardiac catheterization and compare it with degree of elevation of PAP estimated by echocardiography, we used two previously described systems to assess PAP elevation by echocardiogram. The first system conformed with published literature of assessment of PVD in BPD^{3,8} and was defined as: Grade I = $SPAP/SBP < 0.5$, Grade II = $SPAP/SBP 0.5-0.67$ and Grade III = $SPAP/SBP > 0.67$. The second system defined the grades based on previously published criteria to estimate PAP from septal position, Grade I $SPAP/SBP < 0.5$, Grade II = $SPAP/SBP 0.5-0.80$ and Grade III = $SPAP/SBP > 0.80$.¹³

Statistics

Data are expressed as median values and interquartile range. Nonparametric

testing was performed due to small sample size. Agreement between a positive echocardiogram and a positive cardiac catheterization result for PVD was quantified by percent agreement. Wilcoxon rank sum test was used to assess differences between the groups for continuous variables and Kruskal Wallis test was used for ordinal variables. Spearman correlation test were used to evaluate the relation between echocardiographic assessment of right ventricular dimensions, right ventricular function and pulmonary flow dynamics, and cardiac catheterization derived PVRi. Since presence of a PDA or VSD can change the pulmonary artery pressure and flow dynamics irrespective of PVR, we repeated the analysis after excluding patients with these shunts. We separately repeated the assessment of right atrial and right ventricular dimensions after excluding patients with a hemodynamically significant ASD defined as an atrial shunt with a $Q_p:Q_s > 1.2$, determined by cardiac catheterization. Statistical analysis was performed using Stata (version 13, College Station, TX); differences were considered significant if p value < 0.05 .

Results

The indication for cardiac catheterization in twenty five (86%) patients was to assess for pulmonary vascular disease, of which 5 patients were also suspected to have pulmonary vein stenosis. Three patients underwent catheterization for closure of their PDA and one patient for closure of an ASD.

The baseline demographic characteristics of the cohort are shown in Table 1. Median duration between the echocardiogram and cardiac catheterization was 1 day (IQR; 1,4 days). All infants received the same pulmonary vasodilator and vasoactive medication support during both the cardiac catheterization and the echocardiogram. Patients on pulmonary vasodilators were on a stable regimen prior to both studies except one patient who had a 9% increase in treprostinil dose between the two studies (from 57ng/kg/min to 62ng/kg/min). Only one patient was on other vasoactive medication infusions (dopamine and epinephrine), which were at the same doses during both studies. Eight patients (36%) had escalation of respiratory support from spontaneously breathing during the echocardiogram to positive pressure ventilation during cardiac catheterization. No patient had systemic hypertension during their echocardiograms.

The measured and calculated hemodynamic data obtained during cardiac catheterization are shown in Table 2. Twenty-one patients (72%) had a $PVRi \geq 3WU$ and 20 patients (69%) met the updated WHO definition of pulmonary arterial hypertension; one patient had a pulmonary capillary wedge pressure of 18mmHg and a $PVRi$ of 5.3WU and so had mixed pulmonary arterial and venous hypertension. In contrast, using the older WHO definition, only 15 patients (52%) met criteria for pulmonary arterial hypertension. Therefore, 5 patients reclassified as having pulmonary arterial hypertension based on the updated definition. These 5 patients had a mean PAP range of 21-25mmHg and a $PVRi$ range from 3.2WU to 6WU.

Twenty-five patients (86%) had a positive echocardiogram for PVD based on the described criteria. Only six patients (21%) had a measurable TR jet velocity and in 9 patients (31%) the evaluation was performed solely based on the systolic septal motion. Fifty-two percent (15/29) of the cohort had either a VSD or a PDA. (Figure 2)

Using only PVRi to define PVD, patients with a false positive echocardiographic assessment (n=6) had measured mean PAP ranging from 19.5mmHg -40mmHg and PVRi ranging from 1.7WU - 3WU. Five of the six patients had a PDA and the sixth had a VSD. Using the same cutoff value of a PVRi >3WU, two patients had a false negative echocardiogram. One had a small PDA, with mean PAP of 21mmHg, SPAP/SBP by catheterization = 0.5 and a PVRi of 4.4WU. The second patient had a TR jet velocity of 2.9m/sec, SPAP/SBP = 0.5 by catheterization, mean PAP of 36.5mmHg, and a PVRi of 4WU.

After excluding patients with post tricuspid valve shunts (PDA only or VSD \pm PDA), the agreement between echocardiographic assessment and cardiac catheterization derived $\text{PVRi} > 3 \text{ WU} \times \text{m}^2$ was markedly enhanced (Figure 3B and C). Using the PVD definition of $\text{PVRi} > 3 \text{ WU} \times \text{m}^2$, the sensitivity and specificity and accuracy (proportion of infants correctly classified) of echocardiography for PVD is shown in Table 3; accuracy was enhanced after excluding patients with post tricuspid valve shunts, with narrowing confidence intervals despite the smaller number of included patients.

There was only fair agreement between the echocardiographic estimation and the invasively measured grading of the PAP to SBP ratio, which was similar regardless of the classification scheme used. (Figure 4) Echocardiography demonstrated both under- and over-estimation of the systolic PAP to systolic systemic pressure ratio, although inaccuracies by echocardiography were no greater than one grade difference from direct measurements by cardiac catheterization.

There were no significant differences between patients with a $PVRi \geq 3$ and those with a $PVR < 3$ in any of the echocardiographic variables measured (Table 4). Of note, patients with mid-systolic notching of the PA Doppler pattern had a $PVRi$ range of 8.9WU to 13.1WU. Overall, for patients with any shunt by echocardiogram, $PVRi$ was variable, with elevated $PVRi$ in some infants with exclusive left-to-right shunts by echocardiography, and normal $PVRi$ in two patients with bidirectional flow via PDA (Table 5).

There were no substantial correlations (ρ -0.1 – 0.28) between structural or functional echocardiographic assessments and $PVRi$ from cardiac catheterization (data not shown). After excluding patients with PDA ($n=11$), there were significant positive correlations between the right ventricular myocardial performance index, right ventricular systolic to diastolic time index and the ratio of right ventricular to left ventricular diameter at end-systole and $PVRi$, and a trend towards an inverse correlation between pulmonary artery acceleration time and $PVRi$ (Figure 5A-D). After further excluding patients ($n=3$) with a hemodynamically significant ASD,

there was also a trend towards a positive correlation between RV end diastolic area and PVRi (Figure 5E).

Discussion

In this study we found only fair-to-moderate agreement between an assessment of elevated PAP using multiple echocardiographic variables and classification of pulmonary hypertension from catheter-based calculation of PVRi in former preterm infants with BPD. Further, we could not identify any substantial correlation between PVRi and multiple echocardiographic measurements of right heart and pulmonary vascular structure and function except after exclusion of data from patients with post tricuspid valve shunts or hemodynamically-significant ASD. We did demonstrate that using the updated WHO definition of pulmonary arterial hypertension with a mean PAP $>20\text{mmHg}$ reflects a PVRi $>3\text{WU}$ better than the cut off mean PAP of 25mmHg used in the prior definition, although utility of echocardiogram remained only fair for this study population.

Mourani and colleagues previously evaluated the clinical utility of echocardiography in diagnosing pulmonary hypertension in infants and young children with lung disease, including BPD.⁸ In the current study, the duration between cardiac catheterization and echocardiography was shorter, at a median of 1 day, and as a result, we had consistent pulmonary vasodilator therapy during the two studies. Similar to the prior study, we utilized multiple echocardiographic measurements to evaluate for elevated

PAP, although we allowed for infants to be classified by any of the variables that might assess pressure, increasing the proportion of echocardiograms that were positive for PVD. In contrast, Mourani et al evaluated single abnormal echocardiographic assessments, or concurrent multiple echocardiographic abnormalities. Finally, we evaluated utility of echocardiography for detection of elevated PVRi, as well as severity classification based on pressure measurements alone, whereas the prior study used PAP only for the definition of PH.^{7,8} Despite these differences, our findings are similar to the utility of single echocardiographic measurements previously demonstrated, with high sensitivity and low specificity for our entire cohort. These characteristics are useful for a screening test, but the low specificity limits utility as a diagnostic test.

However, the utility of the screening echocardiogram in this patient population is more apparent when infants with post tricuspid valve shunts are excluded. Although echocardiography with the exclusion of PDA only still has modest specificity (66.7%), the exclusion of echocardiograms with either PDA or VSD raises specificity to 100% while still demonstrating good sensitivity. Post tricuspid valve shunts transmit the systemic pressure to the pulmonary circulation regardless of the presence or absence of PVD.

Therefore, the agreement between echocardiographic assessment of PAP and calculated PVRi was markedly improved after excluding patients with post-tricuspid valve shunts. It is also important to note that the patients with a false negative echocardiographic assessment had truly borderline

elevation of PVRi and systolic PAP/SBP ratio. Echocardiography did not miss any patients with severe elevation of PVRi. However, echocardiography performed poorly when grading the degree of PAP elevation, as was shown in prior studies.⁸

We have identified variables that correlate with the degree of elevation of PVRi in patients without post tricuspid valve shunts. These variables may have value if studied prospectively in grading the degree of PVD. Namely the RV MPI, RV SDI, RV-LV diameter ratio at end systole, the direction of flow in post tricuspid valve shunts, the shape of the pulmonary artery Doppler signal and the pulmonary artery acceleration time. These variables have been studied, although not exclusively in BPD patients.¹⁷⁻²¹ Levy et al, in a cohort of older children, showed that PAAT correlated well with PVR and proposed a cut off PAAT <90msec for prediction of a PVRi >3WU.⁹ However, in a subsequent report by the same author, the PAAT was shortened at age one year in all preterm infants born <1000gm regardless of their BPD or prior pulmonary hypertension status.²² Our results agree with the author's first report, with higher PVR values associated with shorter pulmonary artery acceleration time. Using a cut off value of PAAT < 90msec to diagnose PVD in patients without a post tricuspid valve shunt in our cohort, classified 12/14 (86%) patients as correctly having PVD and misclassified only 2 patients (one with a significant ASD shunt). Future studies should address development of cut off values for the aforementioned variables that correlate with the presence of PVD or the severity of elevation of PVR.

Our study has a relatively small sample size, yet is the largest cohort of only BPD patients with multiple quantitative measurements applied to the whole cohort. However, the small sample size did limit our ability to identify statistically significant differences in various echocardiographic variables between those infants with PVD versus those without PVD. In particular, we are unable to further assess the importance of a notched PA Doppler pattern. Despite our small cohort, we do demonstrate that purely left to right shunts do not exclude pulmonary vascular disease and that bidirectional PDA shunts do not always imply elevated pulmonary vascular resistance. Further, although there is some heterogeneity in our cohort with respect to the severity of BPD and baseline pulmonary vasodilator therapy, we present our retrospective data in a manner that can be readily applied to any group of former preterm infants at risk for PVD: echocardiograms and catheterizations were performed within a short interval with the same pulmonary vasodilator therapy, multiple measurements were used to classify PVD by echocardiography, and two different definitions each of both PVD and the severity of PH by catheterization were evaluated. The effect of sedation or general anesthesia on the correlations between echocardiographic and catheterization assessments of pulmonary hemodynamics cannot be quantified using our study design. Medications used for sedation during cardiac catheterization may have different effects on the systemic and the pulmonary circulations. Despite that, similar to other studies of PH in BPD patients ^{3,8}, we used the SPAP/SBP ratio to grade the severity of PH mainly

because 30% of our cohort only had septal flattening as a sign of PH.

Conclusion

Echocardiography can be a useful screening tool for PVD in former preterm infants with BPD. Utility of echocardiography is limited for the presence or severity of PVD, however, when a post tricuspid valve shunt is present. Our data suggest that cardiac catheterization remains an important diagnostic test to assess severity of both PVD and pulmonary hypertension using pressure criteria. Future studies should address the potential value of specific echocardiographic measurements for non-invasive assessment of calculated PVRi in this population, with consideration of RV myocardial performance, end-systolic ventricular dimensions, and PAAT measurements.

TABLE 1. Characteristics of the study population (n=29)

<i>Baseline characteristics</i>	
Gestational age at birth (weeks and days)	25 5/7 (24 4/7 – 26 6/7)
Birth weight (grams)	610 (520-705)
Male sex	17 (59%)
<i>Characteristics at 36 weeks of corrected GA</i>	
<u>Respiratory support</u>	
None	0 (0%)
≤ 2l nasal cannula	2 (7%)
> 2l nasal cannula	5 (17%)
Nasal CPAP or RAM cannula	13 (43%)
Invasive mechanical ventilation	5 (17%)
Unknown	4 (14%)
<u>Oxygen requirement > 30%</u>	
Overall	20 (69%)
Of those with ≤ 2l nasal cannula	1 (50%)
Of those with > 2l nasal cannula	3 (60%)
Of those on CPAP or RAM cannula	9 (69%)
Of those on invasive mechanical ventilation	5 (100%)
<i>Characteristics of study population at time of cardiac catheter procedure</i>	
Postnatal age in days	157 (121-219)
Postmenstrual age	49 0/7 (42 4/7 – 55 6/7)
Weight in grams	3700 (3100-5000)
<u>Medications</u>	
Sildenafil	10(33%)
Bosentan	2(7%)
Prostanoid	2(7%)
iNO	4(13%)
<u>Respiratory support</u>	
None	1 (3%)
Nasal cannula ≤ 2lpm	7 (24%)
FiO2	1.0 (0.4-1.0)
Nasal cannula > 2 lpm	4 (14%)
FiO2	0.4 (0.3-0.5)
Nasal CPAP or RAM cannula	10 (35%)
FiO2	0.4 (0.3-0.5)
Conventional mechanical ventilation	7 (24%)
FiO2	0.5 (0.4-0.9)
<u>Anesthesia for procedure for infants with natural airway (n= 22)</u>	
Spontaneously breathing	14 (64%)
Positive pressure ventilation	8 (36%)

Continuous variables are shown as median and interquartile range, dichotomous or categorical variables as n and proportions (%)

TABLE 2. Hemodynamic variables obtained by cardiac catheterization

Variables (N=29)	Median (Q1, Q3)
Right atrial mean pressure (mmHg)	7 (6,8)
Left atrial mean pressure (mmHg)	9 (7,10)
Systolic PAP (mmHg)	47 (39,54.5)
Mean PAP (mmHg)	32 (25,39.5)
Diastolic PAP (mmHg)	18.8 (13, 24)
Systolic PAP/SBP ratio	0.58 (0.52,0.74)
PVRi (WU)	4.6 (3,6.6)
PVRi/SVRi	0.31 (0.22,0.58)
Q_p (mL/min/m²)	4.25 (3.2,5.6)
Q_p:Q_s	1.1 (1,1.6)

PAP = pulmonary artery systolic pressure, PVRi= pulmonary vascular resistance indexed to body surface area, Q_p = pulmonary blood flow, Q_s = systemic blood flow, SBP = systolic systemic blood pressure, SVRi = systemic vascular resistance indexed to body surface area

TABLE 3. Accuracy, sensitivity and specificity of echocardiography in diagnosing pulmonary vascular disease by cardiac catheterization.

	Accura cy	Sensitiv ity	Specific ity	AUC (CI)
Prior WHO Definition: $PVRI \geq 3WU$, mean PAP $\geq 25mmHg$, PCWP $\leq 15mmHg$				
Positive echocardiogram for PH (n=29)	57	56	75	0.65 (0.39-0.92)
Updated WHO Definition*: $PVRI \geq 3WU$, mean PAP $> 20mmHg$, PCWP $\leq 15mmHg$				
Positive echocardiogram for PH (n=29)	69	72	50	0.61 (0.31-0.9)
$PVRI \geq 3WU$				
Positive echocardiogram for PH (n=29)	72	90.5	25	0.58 (0.39-0.76)
Septal position (n=29)	69	85.7	25	0.61 (0.42-0.79)
Positive echocardiogram for PH excluding patients with PDA (n=18)	89	93.3	66.7	0.8 (0.52-0.94)
Septal position excluding patients with PDA (n=18)	83	86.7	66.7	0.8 (0.52-0.94)
Positive echocardiogram for PH excluding patients with PDA & VSD (n=14)	93	91.7	100	0.96 (0.66-0.99)
Septal position excluding patients with PDA & VSD (n=14)	93	91.7	100	0.96 (0.66-0.99)

*WHO definition updated following the study period, at the 6th World Symposium on Pulmonary Hypertension, Nice 2018
AUC = area under the curve, CI = confidence interval, PAP = pulmonary artery pressure, PCWP = pulmonary capillary wedge pressure, PH = pulmonary hypertension, PVRI= pulmonary vascular resistance indexed to body surface area

TABLE 4. Echocardiographic variables in patients with and without pulmonary vascular disease based on a cutoff PVRI of 3 WU

	PVRI ≥ 3 (n=21)*	PVRI ≤ 3 (n=8)*	P value
Quantitative Dimensions			
RA Area (cm ²)	2.7 (2.3-4.4)	3.3 (3-3.7)	0.33
RA Area indexed (cm ² /m ²)	13.1 (12.3-15.5)	14.1 (13.7-14.8)	0.31
RV basal diameter (cm)	16.1 (15.7-18.1)	19 (15.7-21.3)	0.07
RV mid diameter (cm)	12.8 (11.8 - 15.1)	14.4 (11.9 - 16.7)	0.31
RV area end diastole (cm ²)	3.3 (3 - 4.2)	4.4 (3.3 - 5)	0.17
RV area end diastole (Z score >2)	4.7% (1/21)	37% (3/8)	0.05
RV area end systole (cm ²)	2 (1.7 - 2.7)	2.4 (2 - 3.2)	0.34
RV:LV end systolic diameter ratio	1.1 (0.9 - 1.34)	1.2 (1.16 - 1.42)	0.44
RVOT diameter (cm)	0.9 (0.8 - 1)	0.9 (0.8 - 1)	0.49
Main PA diameter (cm)	1 (0.9 - 1.2)	1 (1.1 - 1.2)	0.79
Right PA diameter (cm)	0.5 (0.5 - 0.7)	0.5 (0.6 - 0.7)	0.54
Left PA diameter (cm)	0.5 (0.4 - 0.6)	0.5 (0.5 - 0.7)	0.56
Qualitative Dimensions			
RV Hypertrophy			0.73
no	33% (7/21)	37.5% (3/8)	
mild	62% (13/21)	62.5% (5/8)	
moderate	5% (1/21)	0	
RV dilation			0.57
no	19% (4/21)	12.5% (1/8)	
mild	47.5% (10/21)	37.5% (3/8)	
moderate	24% (5/21)	50% (4/8)	
severe	9.5% (2/21)	0	
Function			
TAPSE (cm)	1 (0.8 - 1.3)	1.1 (0.9 - 1.2)	0.7
TAPSE z score	-1 (-1.7 - 1.1)	1.8 (-1.2 - 3.4)	0.21
RV FAC (%)	38 (36 - 40)	39 (38 - 43)	0.38
RV SDI (blood pool)	1.9 (1.6 - 2.1) (n=17)	1.8 (1.6 - 1.9) (n=5)	0.32
RV SDI (TDI)	1.9 (1.6 - 2) (n=15)	1.8 (1.2 - 2.1) (n=6)	0.53

RV s' TDI (cm/sec)	8.3 (7.7 - 10.7) (n=15)	8.3 (8 - 10) (n=6)	0.97
RV MPI	0.32 (0.26 - 0.38) (n=14)	0.24 (0.19-0.42) (n=4)	0.34
RV CO indexed (L/min/m ²)	4.3 (2.9 - 6.3) (n=19)	4.2 (2.7 - 6)	0.96
Pulmonary flow dynamics			
PAAT (msec)	53 (45 - 82) (n=19)	89 (43 - 105)	0.31
PAAT/RVET	0.28 (0.25 - 0.43) (n=19)	0.44 (0.24 - 0.54)	0.3
PA Doppler pattern	Normal 37% (7/19)	Normal 62.5% (5/8)	0.14
	Triangle 42% (8/19)	Triangle 37.5% (3/8)	
	Notched 21% (4/19)	Notched 0	

Data are median (IQR) or percentage

*unless otherwise noted

CO = cardiac output, FAC = fractional area change, LV= left ventricle, MPI = myocardial performance index, PA = pulmonary artery, PAAT= pulmonary artery acceleration time, RA = right atrium, RV = right ventricle, RVOT = right ventricular outflow tract, SDI = systolic to diastolic time index, TAPSE = tricuspid annular plane excursion, TDI = tissue Doppler imaging

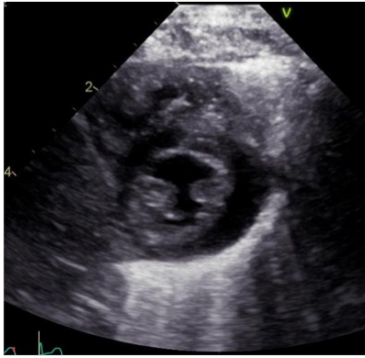
Table 5. PVRI values grouped by shunt flow direction

Shunt	Direction of flow (N)			P value
PVRI median (Q1,Q2)				
Inter-atrial communication	L to R (n=22)	Bidirectiona l (n=5)	R to L (n=1)	0.14
	4.5 (2.8,6)	5.8 (4.2,10.1)	13.1	
PDA	L to R (n=8)	Bidirectiona l (n=2)	R to L (n=1)	0.18
	4.3 (2.5,5.5)	1.7 /3	8.9	
VSD	L to R (n=3)	Bidirectiona l (n=1)	R to L (n=1)	0.2
	2.8-4.6	12.6	8.9	

L to R = left to right, PVRI= pulmonary vascular resistance indexed to body surface area, R to L = right to left

Figure 1. Parasternal short axis images of three different septal positions at end systole depicting the different grades of pulmonary hypertension.

No systolic septal flattening
SPAP/SBP < 0.5



Systolic septal flattening
SPAP/SBP = 0.5-0.8



Septum bulges into LV
SPAP/SBP > 0.8



All images are at end systole. LV = left ventricle, SBP = systolic blood pressure,
SPAP = systolic pulmonary artery pressure

Figure 2. Flow chart of echocardiographic screening and cardiac catheterization results based on presence or absence of a PDA or VSD

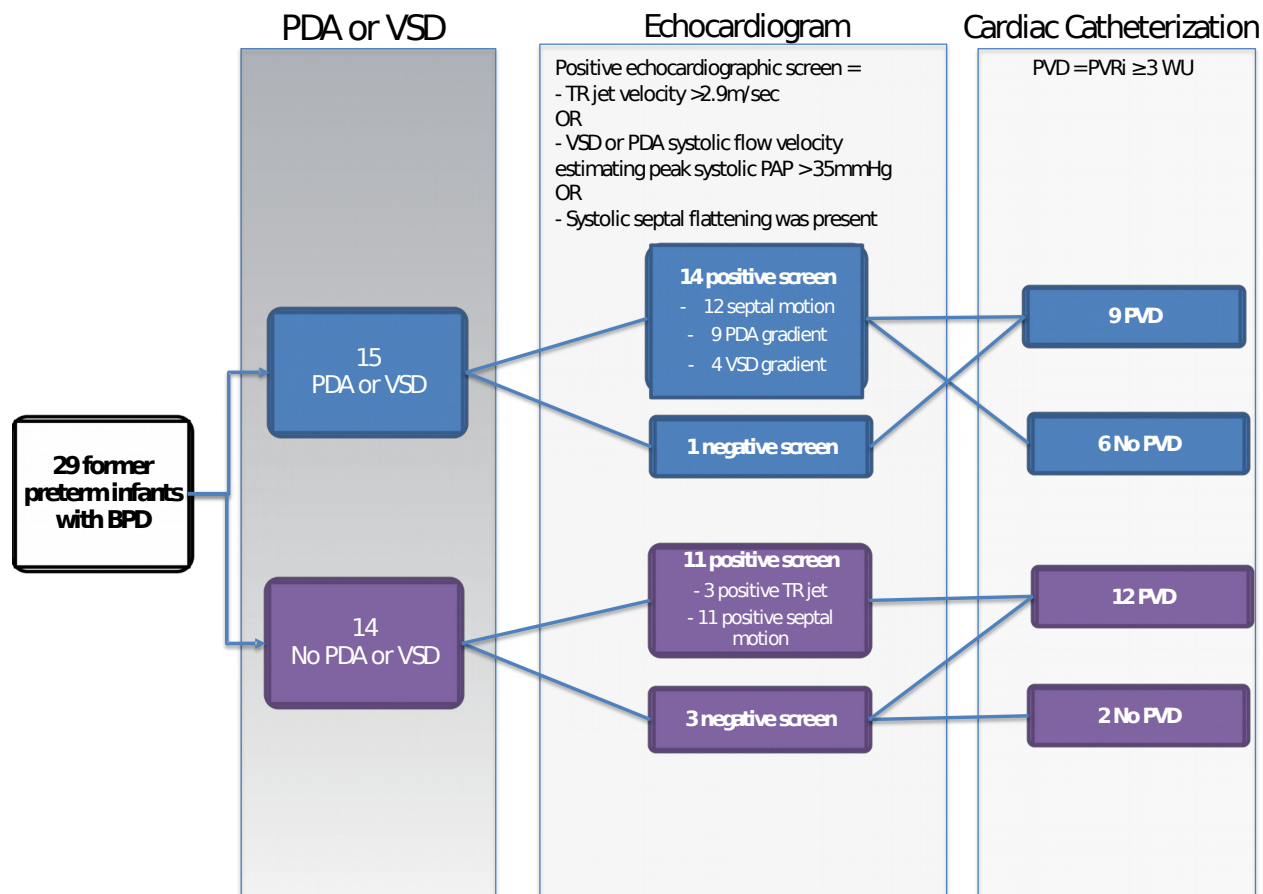
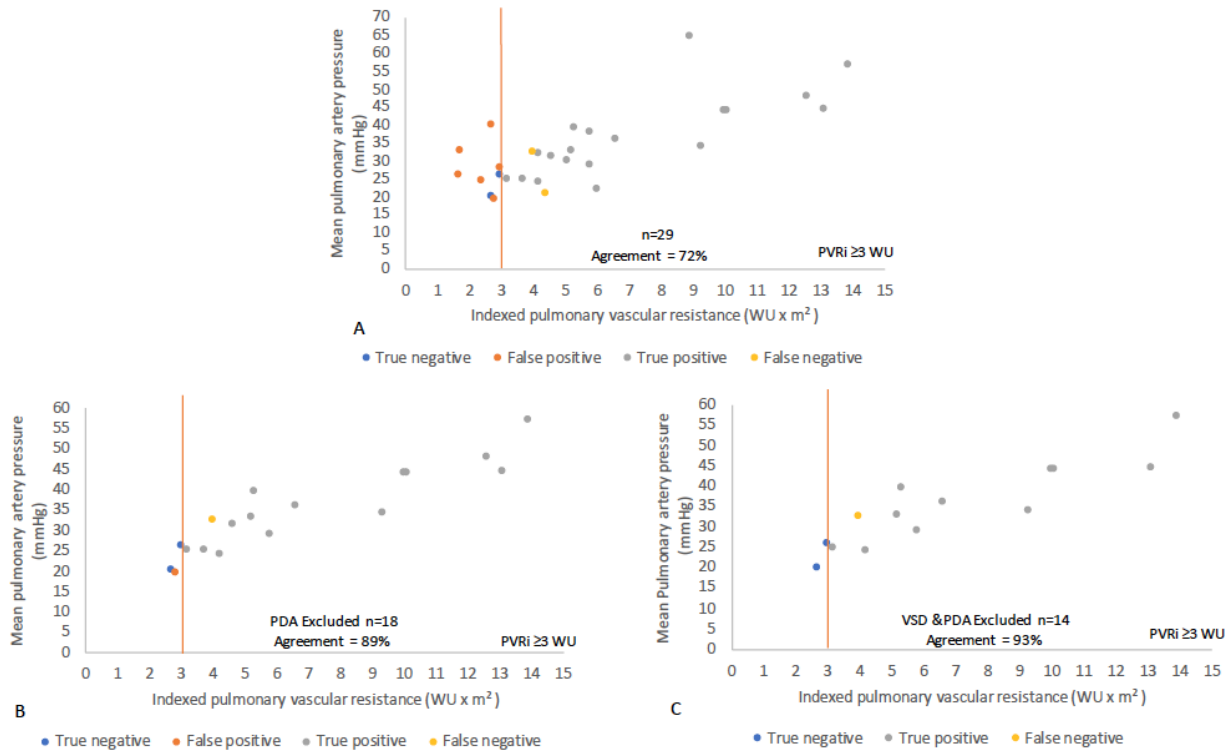
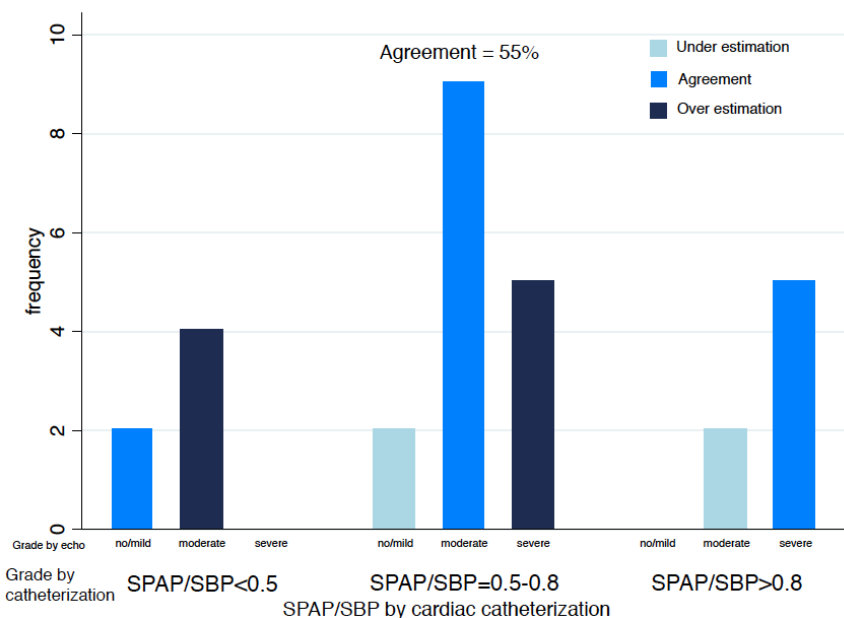
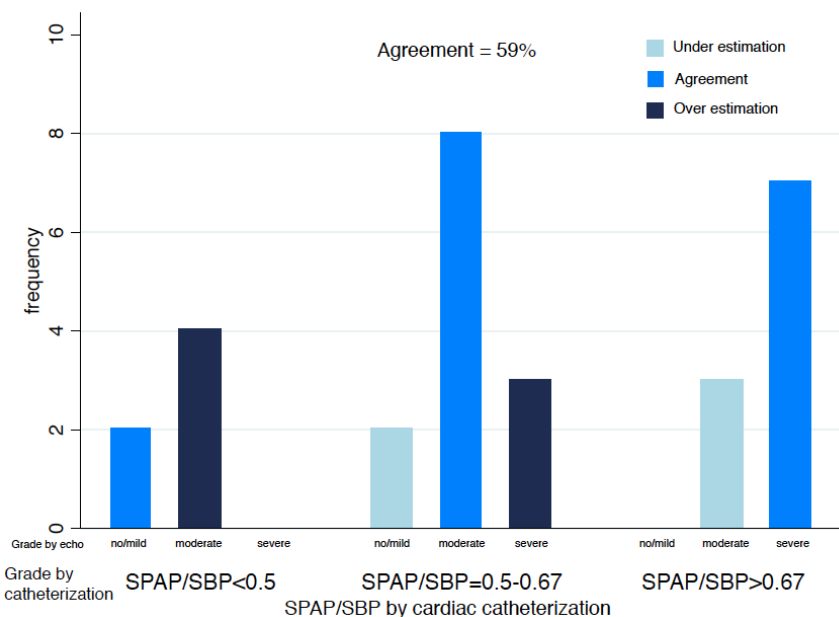


Figure 3. Agreement between echocardiographic estimation of elevated pulmonary artery pressure and cardiac catheterization derived $PVRi \geq 3 \text{ WU} \times \text{m}^2$ in A) all cohort B) cohort after excluding patients with PDA C) cohort after exclusion all patients with post tricuspid valve shunts.



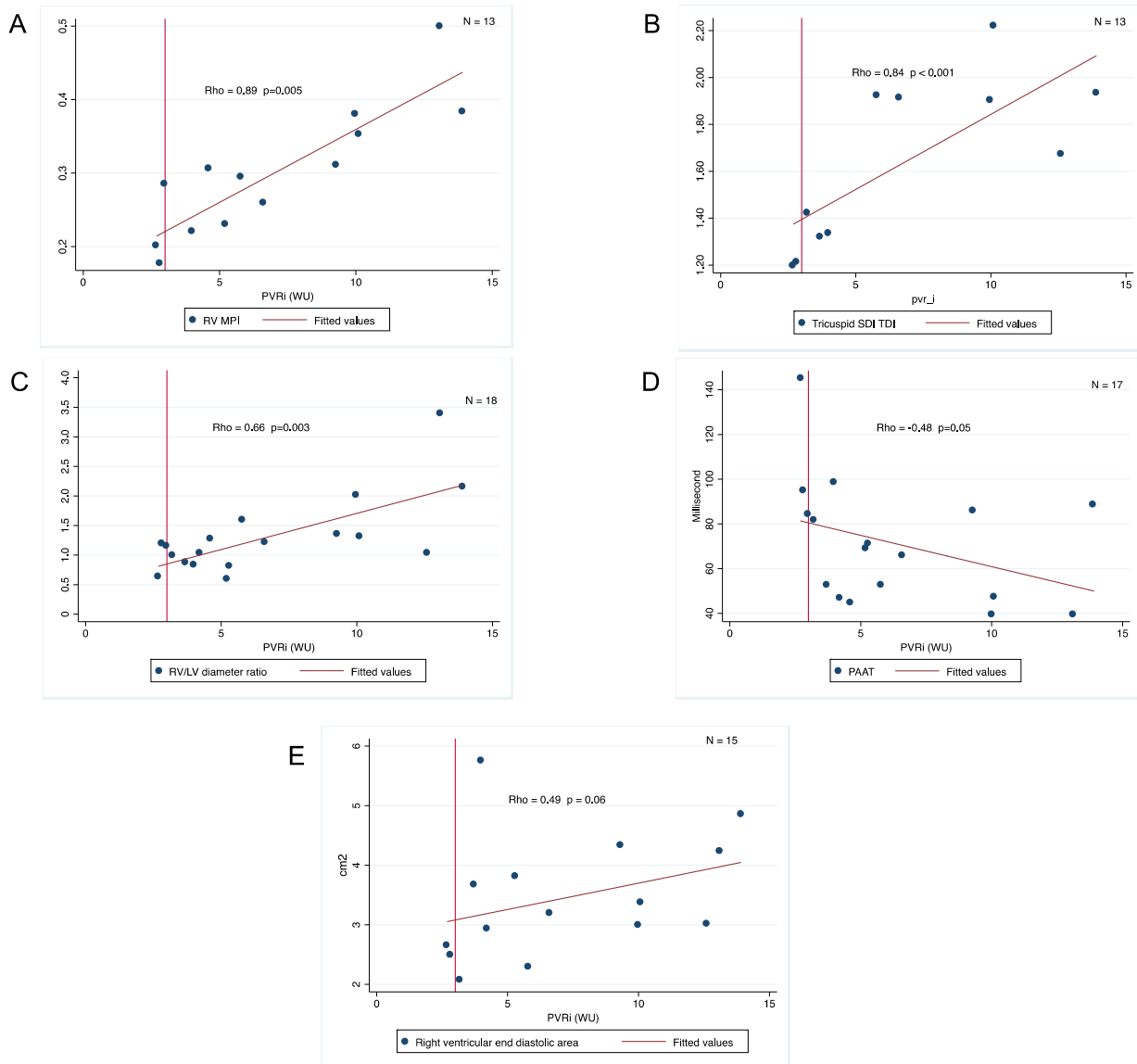
$PVRi$ = pulmonary vascular resistance indexed to body surface area

Figure 4. Bar graph showing poor agreement between echocardiographic and cardiac catheterization grading of pulmonary artery pressure using two different classification systems A) classification from published literature in infants with bronchopulmonary dysplasia, B) classification from septal motion literature. There is over estimation and under estimation of no/mild and severe pulmonary hypertension respectively. There is both under and over estimation of moderate pulmonary hypertension.



SPAP/SBP = ratio of systolic pulmonary artery pressure to systemic systolic blood pressure

Figure 5. Correlation between PVRI and A) RV MPI, B) RV SDI by TDI, C) RV/LV diameter ratio at end systole, D) PAAT, in the absence of a PDA. E) Correlation between RV end diastolic area and PVRI in the absence of PDA and a hemodynamically significant ASD.



Individual observations are plotted. Vertical lines represent PVRI = 3WU. PAAT = pulmonary artery acceleration time, PVRI = pulmonary vascular resistance indexed to body surface area, RV/LV diameter ratio = right ventricular to left ventricular diameter ratio at end systole, RV MPI = right ventricular myocardial performance index, RV SDI TDI = right ventricular systolic to diastolic time index measured by tissue Doppler imaging

References

1. Abman SH, Hansmann G, Archer SL, Ivy DD, Adataia I, Chung WK, et al. Pediatric Pulmonary Hypertension: Guidelines From the American Heart Association and American Thoracic Society. *Circulation* 2015;132:2037-99.
2. Khemani E, McElhinney DB, Rhein L, Andrade O, Lacro RV, Thomas KC, et al. Pulmonary artery hypertension in formerly premature infants with bronchopulmonary dysplasia: clinical features and outcomes in the surfactant era. *Pediatrics* 2007;120(6):1260-9.
3. Krishnan U, Feinstein JA, Adataia I, Austin ED, Mullen MP, Hopper RK, et al. Evaluation and Management of Pulmonary Hypertension in Children with Bronchopulmonary Dysplasia. *J Pediatr* 2017;188:24-34.
4. Ge Z, Zhang Y, Kang W, Fan D, An F. Noninvasive evaluation of interventricular pressure gradient across ventricular septal defect: a simultaneous study of Doppler echocardiography and cardiac catheterization. *Am Heart J* 1992;124(1):176-82.
5. Ge Z, Zhang Y, Ji X, Fan D, Duran CM. Pulmonary artery diastolic pressure: a simultaneous Doppler echocardiography and catheterization study. *Clin Cardiol.* 1992;15(11):818-24.
6. Ge ZM, Zhang Y, Fan DS, Fan JX, Ji XP, Zhao YX, et al. Reliability and accuracy of measurement of transductal gradient by Doppler ultrasound. *Int J Cardiol.* 1993;40(1):35-43.
7. Groh GK, Levy PT, Holland MR, Murphy JJ, Sekarski TJ, Meyers CL, et al. Doppler Echocardiography Inaccurately Estimates Right Ventricular Pressure in Children with Elevated Right Heart Pressure. *J Am Soc Echocardiogr.* 2014;27(2):163-71.
8. Mourani PM, Sontag MK, Younoszai A, Ivy DD, Abman SH. Clinical utility of echocardiography for the diagnosis and management of pulmonary vascular disease in young children with chronic lung disease. *Pediatrics* 2008;121(2):317-25.
9. Levy PT, Patel MD, Groh G, Choudhry S, Murphy J, Holland MR, et al. Pulmonary Artery Acceleration Time Provides a Reliable Estimate of Invasive Pulmonary Hemodynamics in Children. *J Am Soc Echocardiogr.* 2016;29(11):1056-65.

10. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2001;163(7):1723-9.
11. Lopez L, Colan SD, Frommelt PC, Ensing GJ, Kendall K, Younoszai AK, et al. Recommendations for quantification methods during the performance of a pediatric echocardiogram: a report from the Pediatric Measurements Writing Group of the American Society of Echocardiography Pediatric and Congenital Heart Disease Council. *J Am Soc Echocardiogr*. 2010;23(5):465-95.
12. Musewe NN, Smallhorn JF, Benson LN, Burrows PE, Freedom RM. Validation of Doppler-derived pulmonary arterial pressure in patients with ductus arteriosus under different hemodynamic states. *Circulation* 1987;76(5):1081-91.
13. King ME, Braun H, Goldblatt A, Liberthson R, Weyman AE. Interventricular septal configuration as a predictor of right ventricular systolic hypertension in children: a cross-sectional echocardiographic study. *Circulation* 1983;68(1):68-75.
14. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr*. 2010;23(7):685-713.
15. Rosenzweig EB, Abman SH, Adataia I, Beghetti M, Bonnet D, Haworth S, et al. Paediatric pulmonary arterial hypertension: updates on definition, classification, diagnostics and management. *Eur Respir J*. 2019 Jan;53(1):1801916.
16. Simonneau G, Robbins IM, Beghetti M, Channick RN, Delcroix M, Denton CP, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2009;54(1 Suppl):S43-54.
17. Alkon J, Humpl T, Manlhiot C, McCrindle BW, Reyes JT, Friedberg MK. Usefulness of the Right Ventricular Systolic to Diastolic Duration Ratio to Predict Functional Capacity and Survival in Children With Pulmonary Arterial Hypertension. *Am J Cardiol*. 2010;106(3):430-6.
18. Lopez-Candales A, Edelman K. Shape of the right ventricular outflow Doppler envelope and severity of pulmonary hypertension. *Eur Heart J - Cardiovasc Imaging*. 2012;13(4):309-16.

19. Bapat R, Aggarwal S, Natarajan G. A right-to-left or bidirectional ductal shunt in preterm neonates: grave implication? *Am J Perinatol*. 2011;28(9):709-14.
20. Patel N, Mills JF, Cheung MMH. Use of the myocardial performance index to assess right ventricular function in infants with pulmonary hypertension. *Pediatr Cardiol*. 2009;30(2):133-7.
21. Jone PN, Hinzman J, Wagner BD, Ivy DD, Younoszai A. Right Ventricular to Left Ventricular Diameter Ratio at End-Systole in Evaluating Outcomes in Children with Pulmonary Hypertension. *J Am Soc Echocardiogr*. 2014;27(2):172-8.
22. Levy PT, Patel MD, Choudhry S, Hamvas A, Singh GK. Evidence of Echocardiographic Markers of Pulmonary Vascular Disease in Asymptomatic Infants Born Preterm at One Year of Age. *J Pediatr*. 2018;197:48-56.

Online supplement

TABLE 1. Two-dimensional, blood pool and tissue Doppler variables collected in the study.

Two Dimensional measurements:
<ul style="list-style-type: none"> • Right atrial area at end systole from apical 4 chamber view (cm²) • Right ventricular basal diameter at end diastole from apical 4 chamber view (cm) • Right ventricular mid-cavity diameter at end diastole from apical 4 chamber view (cm) • Right ventricular outflow tract diameter from short axis view of the cardiac base (cm) • Right ventricular diameter at end systole from short axis view at the papillary muscle level. (cm) • Right ventricular area at end diastole from apical 4 chamber view (cm²) • Right ventricular area at end systole from apical 4 chamber view (cm²) • Tricuspid annular plane systolic excursion (cm) • Main and branch pulmonary artery diameters from short axis of the cardiac base (cm) • Left ventricular diameter at end systole from short axis at the papillary muscle level. (cm)
Blood pool Doppler measurements
<ul style="list-style-type: none"> • Tricuspid regurgitation jet peak velocity (m/sec) • Tricuspid valve inflow duration (msec) • Blood pool cycle length (msec) • Pulmonary artery acceleration time (PAAT) (msec) • Right ventricular ejection time (RVET) (msec) • Right ventricular ejection velocity time integral (RV VTI) (cm) • Peak systolic velocity of flow across PDA or VSD (m/sec)
Tissue Doppler measurements
<ul style="list-style-type: none"> • Lateral tricuspid valve annular peak systolic (s') velocity (m/sec) • Lateral tricuspid valve annular filling time duration • Tissue Doppler cycle length (msec)
Calculations
<ul style="list-style-type: none"> • To convert velocity to pressure gradients, a simplified Bernoulli equation was used Pressure gradient = $4 \times \text{velocity}^2$ • Right ventricular fractional area change (RV FAC): (right ventricular area at end diastole - right ventricular area at end systole) / right ventricular area at end diastole • Pulmonary blood flow = $(\pi \times (\text{RVOT diameter}/2)^2 \times \text{RV VTI}) \times \text{heart rate}$ • PAAT corrected to heart rate = PAAT/RVET

<ul style="list-style-type: none">• Systolic to diastolic time index: $(\text{cycle length} - \text{filling time}) / \text{filling time}$
Qualitative assessment
<ul style="list-style-type: none">• Right ventricular dilation• Right ventricular hypertrophy• Septal motion• Pulmonary artery Doppler pattern (normal / triangular / mid-systolic notch)